REMARKS

Upon entry of the amendments to the claims presented herein, claims 38, 41, 42, 44, 54, 55, and 61 are pending in the instant application. Claims 38 and 54 are amended, and claims 1-37, 39-40, 43, 45-53, 56-60, and 62-68 are canceled. Applicants reserve the right to pursue the subject matter of these claims in a continuing or divisional application. Support for the amended claims may be found throughout the specification as filed, and at least at page 2, line 32 to page 3, line 5; at page 16, lines 10-13; and in Example 11 (Figure 16). No new matter is added.

Statement of Substance of Examiner Interview

Applicants' representative would like to thank the Examiner for the courtesies extended during the interview conducted on January 20, 2010. The rejections set forth under the issues raised in the Office Action mailed October 15, 2009 with respect to 35 U.S.C. § 103(a) were discussed during the interview. Applicants' representative emphasized that neither Richards et al., (Vaccine, 15(10): 1065-1069 (1997); "Richards") nor WO 97/02045 to Williams *et al.* ("Williams") teach or suggest the use EtxB in a method of generating a T lymphocyte cell-mediated protective immune response against a herpes virus infection. Rather, these references concern enhancement of an antibody response[1] or treatment or the prevention of an autoimmune disease.[2] Thus, the combination of these references would not have lead a person of ordinary skill in the art to a method of generating a T lymphocyte cell-mediated protective immune response.

Further, there would be no motivation to combine Richards and Williams at least because Williams teaches away from the present invention. That is, Williams teaches that EtxB protein induces differential effects on lymphocyte populations, including a specific depletion of CD8+ T cells. Specifically, Williams states as follows:[3]

> The basis for all aspects of the present invention is the finding that EtxB (the pure B-subunit of the E. coli heat labile enterotoxin) binds to GM1-ganglioside receptors which are found on the surfaces of mammalian cells, and that this binding induces differential effects on lymphocyte populations, including a specific depletion of CD8+ T cells and an

[1] See *e.g.*, Richards at page 1067, left column, which states as follows: "Enhancement of the antiviral antibody response by the co-administration of cholera toxin."
[2] See *e.g.*, Williams at Abstract.
[3] Williams at page 1, line 34 to page 2, line 6 and page 2, lines 20-28.

> associated activation of B cells. These effects are absent when a mutant EtxB protein lacking GM1 binding activity is employed.
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> Agents in accordance with the present invention have been found to modulate lymphocyte populations leading to the induction of apoptosis in CD8+ T cells, the enhanced activation of CD4+ cells and polyclonal activation of B cells. These events are likely to shift the immune response towards induction of Th2 associated cytokines. Such responses to self or crossreacting antigens are understood to mediate protection for certain autoimmune diseases.

In this regard, Williams relates to the activation of a humoral immune response, rather than the recited T lymphocyte cell-mediated protective immune response.

Rejections under 35 U.S.C. § 103.

The Examiner has rejected claims 38, 41-42, 44, 54-55, 58-59 and 51 under 35 U.S.C. § 103 as being obvious over Richards et al., (Vaccine, 15(10): 1065-1069 (1997); "Richards") in view of WO 97/02045 to Williams *et al.* ("Williams"). Claims 58 and 59 are cancelled. This rejection is therefore moot as applied to these claims. Applicants respectfully traverse with respect to the claims as amended herein.

In order to establish a *prima facie* case of obviousness, the Examiner must consider *all claim limitations* when determining patentability in view of the prior art.[4] Richards does not teach or suggest generating a T-lymphocyte cell-mediated protective immune response comprising co-administering to a mammal a therapeutically effective amount of Escherichia coli heat labile enterotoxin B subunit (EtxB), and an antigen, wherein the EtxB is free from whole toxin and is not linked to the antigen. Primarily, Richards does not relate to the use of EtxB, but rather cholera toxin (Ctx), which is distinct from EtxB. That is, Richards concerns enhancement of an antibody response[5], which is distinct from a T-lymphocyte cell-mediated protective immune response, in the presence of cholera toxin.

Further, the Office Action relies on the teaching in Richards that the "inoculations procedures show that Cholera toxin or subunit B toxin were co-administered with the virus antigen."[6] In fact, Richards teaches that Ctx and CtxB were used in combination.[7] Further, on

[4] See *In re Lowry*, 32 F.3d 1579, 1582 (Fed. Cir. 1994).
[5] See *e.g.*, Richards at page 1067, left column, which states as follows: Enhancement of the antiviral antibody response by the co-administration of cholera toxin."
[6] See Office Action at page 5, line 1-3.

page 1065, right column, lines 7-9, Richards states the following: "Cholera toxin, is one such adjuvant, capable of generating high levels of mucosal IgA and T cell responses." Thus, does not teach or suggest the use of CtxB free from whole toxin. This teaching in Richards reflects the state of the art prior to the present invention that a combination of CtxB with whole Ctx was important for achieving an effective adjuvant. In contrast, the present claims recite that EtxB is free from whole toxin and is not linked to the antigen.

Additionally, the Office Action fails to set forth a reasonable rationale as to why a person of ordinary skill in the art would substitute the use of cholera toxin alone or in combination with the cholera toxin B subunit of Richards with EtxB that is free from whole toxin and that is not linked to the antigen. Williams fails to cure this deficiency of Richards. On page 5 of the Office Action, it is alleged that Williams teaches "the administration of Ctx, CtxB, Etx, or EtxB as being interchangeable." Even if this were true, the combination of Richards and Williams does not produce EtxB necessarily free from whole toxin.

Further, the combination of Richards and Williams does not teach the induction of a T lymphocyte cell-mediated protective immune response. Rather, the combination only provides for the induction of a humoral response. As stated above, Richards concerns enhancement of an antibody response.[8] While Williams does state that EtxB can modulate lymphocyte populations, Williams fails to teach that EtxB can generate a T lymphocyte cell-mediated protective immune response, as required by amended claim 38. In fact, Williams teaches that EtxB induces apoptosis in $CD8^+$ T lymphocytes, and enhances activation of B-cells.[9] Further, Williams teaches the use of EtxB as a vaccine carrier for the treatment of autoimmune disease[10] and for the treatment of T-lymphocyte leukemias.[11] In other words, Williams teaches that EtxB down-regulates cell-mediated immunity which promotes immunoprotection, and up-regulates humoral immunity which *promotes immune tolerance*. In this manner, Williams teaches away from co-administration of EtxB and a viral antigen to produce a T lymphocyte cell-mediated protective

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[7] See Richards at page 1066, left column, under the heading *Inoculations*, which states that Ctx was used alone or in combination with CtxB.
[8] See *e.g.*, Richards at page 1067, left column, which states as follows: "Enhancement of the antiviral antibody response by the co-administration of cholera toxin."
[9] *Id.* at page 2, lines 2-5 and lines 20-24.
[10] *Id.* at page 2, lines 7-28 and page 3, lines 4-15.
[11] *Id.* from page 5, line 27 to page to page 6, line 11.

immune response, as required by independent claim 38. Specifically, Williams states as follows:[12]

> The basis for all aspects of the present invention is the finding that EtxB (the pure B-subunit of the E. coli heat labile enterotoxin) binds to GM1-ganglioside receptors which are found on the surfaces of mammalian cells, and that this binding induces differential effects on lymphocyte populations, including a specific depletion of CD8+ T cells and an associated activation of B cells. These effects are absent when a mutant EtxB protein lacking GM1 binding activity is employed.
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> Agents in accordance with the present invention have been found to modulate lymphocyte populations leading to the induction of apoptosis in CD8+ T cells, the enhanced activation of CD4+ cells and polyclonal activation of B cells. These events are likely to shift the immune response towards induction of Th2 associated cytokines. Such responses to self or crossreacting antigens are understood to mediate protection for certain autoimmune diseases.

Thus, Williams teaches a use for EtxB that induces depletion of CD8+ cytotoxic T-lymphocytes and enhances activation of B-lymphocytes when co-administered with an antigen. Thus, Williams teaches the depletion of cell-mediated immunity (i.e., protective immunity) and the enhancement of humoral immunity (i.e., immune tolerance) by co-administering EtxB with an antigen. As stated above, Richards is concerned with enhancement of an antibody response[13], and therefore neither Richards, Williams, or the combination thereof, would not result in a T-lymphocyte cell-mediated protective immune response according to the present claims.

In view of the above, Applicants respectfully request withdrawal of this rejection.

Rejections under 35 U.S.C. § 112, second paragraph:

The Examiner has also rejected claims 38, 41-42, 44 and 58 under 35 U.S.C. § 112, second paragraph, as being indefinite. According to the Examiner, the term "enhancing" in claim 38 is a relative term which is not defined by the claim, and the specification does not provide a standard of comparison for ascertaining the requisite degree of enhancement.

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[12] Williams at page 1, line 34 to page 2, line 6 and page 2, lines 20-28.
[13] See *e.g.*, Richards at page 1067, left column, which states as follows: Enhancement of the antiviral antibody response by the co-administration of cholera toxin."

Claim 38 has been amended to delete the word "enhancing". As amended, claim 38 recites the phrase "generating the protective immune response". The element "generate" was borrowed from claim 54, which has not been rejected for lack of written description or indefiniteness. The generation of a T-lymphocyte cell-mediated protective immune response (i.e., Th2 associated response) is supported in the specification at page 39, lines 6-34 and in Figures 16 and 17. In addition, Figure 2 shows the generation of T cell proliferation, an indicator of a T-lymphocyte cell-mediated immune response, in cells isolated from mice immunized with EtxB and HSV-1 antigen. Figure 3 shows similar results with mice immunized different combinations of doses of EtxB and HSV-1 antigen.

Claim Objections:

Claims 58-59 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of the previous claim. According to the Examiner, claims 58-59 are duplicative of claims 41 and 42. Claims 58-59 have been cancelled herein, rendering this objection moot.

CONCLUSION

Applicants submit that the claims as here amended put the application in condition for allowance, and such action is respectfully requested. Should any questions or issues arise concerning the application, the Examiner is invited and encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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